

## Bioacoustic-enabled patterning of human iPSC-derived cardiomyocytes into 3D cardiac tissue.

**Journal:** Biomaterials

**Publication Year:** 2017

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**PubMed link:** 28376365

**Funding Grants:** Curriculum Development and Implementation of Stem Cell Technology and Laboratory Management Emphasis in an Established MS Biotechnology and Bioinformatics Program at California State University Channel Islands and Co-development of a GE Course on Stem Cell, Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure, Macaca mulatta as advanced model for predictive preclinical testing of engineered cardiac autografts and allografts

### Public Summary:

The generation of three-dimensional (3D) functional tissues that can restore the structure and/or function of damaged myocardium is a central goal in cardiac regenerative medicine. In addition, the creation of high-fidelity in vitro tissue models may improve our understanding of various biological processes including heart development, myocardial damage, and disease. The creation of 3D tissue constructs that mimic native myocardium requires an appropriate selection of cell source and biomaterial that resembles the native tissue structure and support cell viability, function, electromechanical integration with host tissue, and vascularization. To date, majority of technologies that enable control over spatial cell arrangement in 3D tissue constructs are based on assembly of cell-encapsulating microscale hydrogels, seeding cells in scaffolds with defined architecture, and additive manufacturing/3D bioprinting techniques. While these techniques have been successfully used in a wide range of applications including bone and skin regeneration, gene delivery, and cell differentiation, they are not yet able to achieve spatially-controlled, physiologically-relevant cell packing densities, comparable to that in the native cardiac tissue for cardiovascular applications. Using the Faraday wave principle to induce patterning in liquid medium, we recently demonstrated rapid and dynamic aggregation of microscale objects (e.g., cell spheroids) into diverse sets of geometric configurations at the air-liquid interface. In this study, by applying Faraday waves to the fibrin prepolymer, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were rapidly patterned (<10 s) into ordered, closely-packed, symmetric 3D constructs. Within the high cell density regions, hiPSC-CMs demonstrated significantly improved viability, intercellular connections, and contractile function (force and motion), in comparison to constructs with random cell distribution. Our results support the feasibility of creating 3D cardiac tissue constructs that approximate native human tissues in their cell density, structure, and function for diverse basic research and clinical applications.

### Scientific Abstract:

The creation of physiologically-relevant human cardiac tissue with defined cell structure and function is essential for a wide variety of therapeutic, diagnostic, and drug screening applications. Here we report a new scalable method using Faraday waves to enable rapid aggregation of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) into predefined 3D constructs. At packing densities that approximate native myocardium (108-109 cells/ml), these hiPSC-CM-derived 3D tissues demonstrate significantly improved cell viability, metabolic activity, and intercellular connection when compared to constructs with random cell distribution. Moreover, the patterned hiPSC-CMs within the constructs exhibit significantly greater levels of contractile stress, beat frequency, and contraction-relaxation rates, suggesting their improved maturation. Our results demonstrate a novel application of Faraday waves to create stem cell-derived 3D cardiac tissue that resembles the cellular architecture of a native heart tissue for diverse basic research and clinical applications.

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